

**REMARKS**

Claims 1-12 presently appear in this case. No claims have been allowed. The official action of February 11, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to substantially homogeneous glycosylated human TNF- $\alpha$  having cytotoxic biological activity, which TNF- $\alpha$  is not labeled with a detectable group, as well as methods for the preparation of such a product by recombinant techniques, compositions and methods of use.

Claims 1, 2, 4, 7, and 12 have been rejected under 35 USC 102(b) as anticipated by Korn. The examiner states that the reference is anticipatory, as it teaches an isolated metabolically labeled TNF for immunoprecipitation experiments. The examiner states that glycosylation is an inherent property of this product. This rejection is respectfully traversed.

Claims 1 and 2 have now been amended to add a proviso that the TNF- $\alpha$  is not labeled with a detectable group. Reference is made to page 9, lines 10-15, of the present specification, which states that the genus of TNF- $\alpha$  in accordance with the present invention includes a species of glycosylated TNF that is labeled with a detectable group, e.g., radioiodinated. Thus, the TNF- $\alpha$  of Korn which is metabolically labeled using  $^{35}\text{S}$ -cysteine is labeled with a detectable  $^{35}\text{S}$  group, just as radioiodination is an

example of a detectable group in the above-cited passage from page 9 of the specification. Note that provisos eliminating disclosed species of a claimed genus to avoid reading on the prior art were held to comply with the written description requirement of 35 USC 112 in *In re Johnson*, 194 USPQ 187, 196 (CCPA 1977).

Accordingly, as the claims have been amended to avoid the anticipation rejection, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 3, 5, 6, and 8-11 have been rejected under 35 USC 103(a) as being unpatentable over Korn in view of Allet. The examiner states that, despite the fact that the prior art was not aware that human TNF- $\alpha$  produced by CHO cells was glycosylated, this is an inherent property of human TNF- $\alpha$  that is inseparable from the compound. The examiner states that the observation that the protein of the prior art contained a specific property is not a basis for patenting a known prior art compound. The examiner states that using a eukaryotic host to produce the protein will avoid the antigenic effects often associated with bacterially grown proteins, and therefore it would have been obvious to modify the methods disclosed in Korn to produce and purify the glycosylated TNF protein, obtain compositions and use it for treating human disease as taught by Allet. This rejection is respectfully traversed.

The examiner's argument about the inherency of glycosylation in CHO cell produced TNF- $\alpha$  is relevant only to anticipation rejections. It is not relevant to the present obviousness rejection because, if the invention as a whole includes unexpected results, such unexpected results can rebut a *prima facie* case of obviousness. The examiner errs in referring to "the protein of the prior art." Korn never produced substantially homogeneous glycosylated human TNF which is not metabolically labeled in CHO cells. The examiner must rely on a secondary reference for isolating such substance. If those of ordinary skill in the art considered that the product of such a combination of references would not be glycosylated and the present inventor discovered the glycosylation properties, this showing of unexpected results would overcome a *prima facie* case of obviousness. Otherwise, it would never be possible to overcome an obviousness rejection by a showing of unexpected results, as the examiner could always state that such unexpected results were inherent in the product of the combination of references.

As to the examiner's argument that, whether or not it was known that the TNF of Korn was glycosylated, it would have been obvious to isolate it from a composition and use it for the treatment of human diseases as taught by Allet because the use of a eukaryotic host to produce the protein would avoid the

antigenic effects often associated with bacterially grown proteins. However, this is not a valid grounds of motivation to isolate the product of Korn, form it into a composition and use it in the treatment of human diseases. If the antigenic effects referred to by the examiner are bacterial contaminants, then switching to CHO cells will not avoid non-human contaminants. If the antigenic effect is the difference between the natural glycoprotein and the bacterially produced unglycosylated protein, there would be no motivation to switch from bacterial production to CHO production because the art thought that TNF was non-glycosylated and there is no reason to believe that, if bacterially produced TNF is antigenic, CHO-produced TNF would be any different. The examiner has not cited any evidence that prior art bacterially produced TNF was known to have problems or that there was any motivation to solve any such problems.

The fact is that there are no practical considerations which would motivate one of ordinary skill in the art to use the techniques of Allet on the product of Korn. Glycosylated TNF is not inherent in the prior art, as the prior art never isolated unlabelled TNF from a recombinant CHO system. TNF can be produced in bacterial systems at relatively less expense than in eukaryotic systems and there would simply be no motivation to produce what would be expected to be the exact same product in the more expensive and complex eukaryotic system of Korn. To

paraphrase *In re Stemniski*, 170 USPQ 343, 347 (CCPA 1971), what on this record - other than abstract, theoretical or academic considerations - would lead one of ordinary skill in the art to produce and isolate TNF from eukaryotic cells? Certainly no practical considerations which promote the progress of useful arts or are of use to society are manifest. When that mythical, but intensely practical, person of ordinary skill in the art has no "practical" reason to change the bacterial recombinant production of TNF to a more expensive CHO system, then it would not be obvious to do so.

The examiner states that one of ordinary skill in the art would have been motivated with reasonable expectation of success to modify the methods of Korn because Allet et al "teach that recombinant TNF can be purified and formulated into compositions for treatment of human diseases." The fact that something can be done does not provide motivation to do so. As stated in *Ex parte Levengood* 28 USPQ2d 1300, 1301-1302 (Bd. Pat. Appl. & Int., 1993):

At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. ... That which is within the capabilities of one skilled in the art is not synonymous with obviousness.

Only the surprising discovery that appears in the present specification, that the human TNF recombinantly produced in CHO cells is glycosylated, provides the requisite motivation. However, this disclosure is not available to the prior art and cannot be used as a source of motivation. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claim 7 has been rejected under 35 USC 112, second paragraph, as being vague and indefinite in the recitation of the term "mutant thereof encodes human TNF- $\alpha$ ".

Claim 7 has now been amended so as to avoid the language that the examiner considered to be ambiguous. Accordingly, this rejection has now been obviated.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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